
Yale Radioactive Drug Research Committee

POLICIES AND PROCEDURES

Table of Contents

I.	Charter	3
II.	Responsibilities	3
III.	Membership	3
IV.	Policies and Procedures.....	4
A.	Meetings.....	4
1.	Quorum	5
2.	Minutes.....	5
3.	Committee Actions	5
B.	Review Procedures	5
1.	Transfer of Applications from YNHH RDRC	5
2.	New Applications.....	5
3.	Amendments to Approved Protocols.....	6
4.	Review of Changes in Radioactive Syntheses	6
C.	Monitoring Procedures	7
D.	Reporting Procedures	7
1.	Adverse Reaction Reporting	7
2.	Quarterly Reporting.....	7
3.	Reporting IRB Renewal and Study Closure	8
4.	FDA Reporting Requirements	8
4.1.	Annual Report	8
4.2.	Special Summary Report	9
4.3.	Protocols with RDRC Oversight involving IND Drugs.....	9
E.	YU-RDRC Record Retention.....	9
APPENDICES		10
Appendix A.	YU-RDRC Membership.....	10
Appendix B.	YU-RDRC Application	10
Appendix C.	Quarterly Report Form	10
Appendix D.	FDA Form 2915.....	10
Appendix E.	FDA Regulations - 21 CFR 361.1	10

Appendix F.	FDA Guidance - The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application, August 2010.	10
Appendix G.	Yale HRPP 940 GD.1, Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation.....	10
REFERENCES.....		10

I. Charter

Food and Drug Administration (FDA) regulations at 21 CFR 361.1 ([Appendix E](#)) entitled "Prescription Drugs For Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used In Research" provide for a mechanism that allows the use of radioactive drugs in human research under certain specific conditions. The human research use of radioactive drugs that meet these specific conditions can be performed without the need for an FDA-approved New Drug Application or an FDA-accepted Investigational New Drug (IND) exemption. Among the conditions specified at 21 CFR 361.1 is the requirement that each research project be approved and monitored by a Radioactive Drug Research Committee (RDRC) that is itself approved by the FDA.

To achieve compliance with these regulations, Yale University submitted an application to charter its Radioactive Drug Research Committee in December 2014. This committee (Radioactive Drug Research Committee No. 206 at Yale University) was approved by the FDA in December of 2014. The YU-RDRC held its first meeting on January 22, 2015.

II. Responsibilities

As outlined in Yale HRPP 940 GD.1, Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation ([Appendix G](#)), the YU RDRC committee is responsible for the review and approval of human subjects research involving radiation exposure and the administration or use of investigational radioactive drugs. This research is typically conducted at the Yale University PET Center. The YU RDRC may occasionally agree to review human subject research protocols involving the use of investigational radioactive drugs without an IND conducted at other institutions.

Radioactive drugs as defined in 21 CFR 310.3(n), may be administered to research participants *without obtaining an IND* when the purpose of the research is to obtain basic information regarding the metabolism such as kinetics, distribution, dosimetry, and localization of a radioactively labelled drug or regarding human physiology, pathophysiology, or biochemistry. These initial studies are considered basic research within the meaning of 21 CFR 361.1. Such basic research studies must be conducted in accordance with 21 CFR 361.1(b), including review by the YU RDRC, which is an FDA required committee.

In order to be a RDRC protocol, the following criteria must be met:

1. The research is basic science research and is not research that is intended for immediate therapeutic, diagnostic, or similar purposes;
2. The research is not research intended to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product);
3. The Investigator must know that the radioactive drug does not cause any clinically detectable pharmacological effect in humans;
4. The number of protocols using the radioactive drug is limited;
5. The number of human subjects in the study is limited; and
6. The protocol does not include drugs that have no documented previous human experience.

If the above criteria are not met, an IND application may instead be submitted to the FDA and the study must be reviewed by the RIDC. For additional information, see [Appendix G](#).

III. Membership

21 CFR 361.1 (c) (1) outlines the requirements for membership of an RDRC. The Committee must be composed of the following individuals: (1) a physician recognized as a specialist in

nuclear medicine; (2) a person qualified by training and experience to formulate radioactive drugs; (3) a person with special competence in radiation safety and radiation dosimetry; and (4) other members qualified in various disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics and radiopharmacy).

The Committee must consist of at least 5 members, and the membership should be diverse enough to permit expert review of the technical and scientific aspects of proposals submitted to the Committee. Note that although one individual may have expertise in more than one category, an individual should only represent one category for the review of protocols. Consultants in other pertinent medical disciplines will be included, as necessary, for review of specific studies. Additionally, an RDRC will include pediatric consultants when it reviews research studies (under the authority of 21 CFR 361.1) that involve subjects less than 18 years of age, as described in Section IV.B.1.

Changes in membership and applications for new members ([Form FDA 2914](#)) must be submitted to the FDA as soon as, or before, vacancies occur and new members are appointed to the YU-RDRC [21 CFR 361.1].

The YU-RDRC has a designated chairperson (“Chair”). A Chair is appointed by the Provost and approved by the YU-RDRC. The Chair signs all applications, minutes, and reports of the YU-RDRC [21 CFR 361.1]. All committee action letters are signed by the Chair. The current *voting* and *non-voting* members of the YU-RDRC and their respective disciplines are outlined in [Appendix A](#).

IV. Policies and Procedures

A. Meetings

The YU-RDRC is required by FDA regulations to meet at least once each calendar quarter. In order to facilitate the timely review of protocols and amendments, the YU-RDRC generally meets monthly (when there is business to transact, but at least once each quarter), typically on the fourth Thursday of each month. Applications and amendments must be submitted for each monthly meeting no later than one week prior to the monthly meeting, (see posted schedule). At the request of the Chair, ad hoc meetings may be convened to review time-sensitive applications or amendments.

The quarterly meeting may be cancelled if, in the quarter, all of the following conditions have been met:

- No subjects have been admitted to any of the approved studies;
- No progress reports have been received on ongoing studies;
- No reports of adverse reactions have been submitted;
- No protocol amendments have been submitted for approval;
- No responses are due on committee recommendations or questions concerning pending research protocols; and
- No new protocols have been submitted.

If the meeting is cancelled, the reason for the cancellation is documented.

The Chair may review and administratively approve unchanged renewal applications that might expire before a scheduled meeting, and minor amendments (those that do not involve changes radiotracer preparation, radiation exposure, or application) throughout the year. The Chair administratively approves some YU-RDRC applications, as described below. A brief

summary of the administrative approval action is distributed to Board members after the action has been taken. The item is reported on the next agenda and minutes for the meeting.

1. Quorum

A quorum is constituted by more than 50% of the voting members of the Committee. However, when applications subject to the requirements of 21 CFR 361.1 are to be considered by the Committee, there must be appropriate voting member representation of the required fields of specialization (i.e., nuclear medicine; formulation of radioactive drugs; and radiation safety/radiation dosimetry).

2. Minutes

Minutes of the meetings of the committee are prepared and signed by the Chair. The minutes include the results of votes on new research protocols and protocol amendments involving the use of human subjects. No member of the Committee votes on a protocol for which he or she participates as an investigator/collaborator, and any such abstentions will be recorded in the minutes. Minutes will be reviewed and approved by the committee members.

3. Committee Actions

Protocols reviewed by the YU-RDRC may be approved, disapproved, or found to be approvable pending IRB approval and pending resolution of other contingencies, if applicable. Investigator responses to substantive contingencies will be reviewed at a subsequently convened Committee meeting. For all protocols involving greater than 30 subjects, the YU-RDRC Chair will notify the FDA of final YU-RDRC approval following resolution of any contingencies and upon notification of final IRB approval.

B. Review Procedures

1. Transfer of Applications from YNHH RDRC

As a first official action, the newly formed YU-RDRC performed a detailed administrative review of all existing protocols previously reviewed, approved, and monitored by the YNHH RDRC. This evaluation included review of transferred materials, documentation and registration of the dates of initial protocol approvals and all amendments. The summary of this review was discussed and approved by the full committee.

The YU-RDRC accepted in transfer the approved radiosyntheses at the PET Center from the YNHH-RDRC for all active protocols.

2. New Applications

As all new applications will undergo full-committee review by the YU-RDRC, the more detailed form, “**Application to Involve Human Subjects in Biomedical Research that Includes use of Radioactive Drugs not covered under an IND (2015-1)**” (**Appendix B**), must be used. Additional documents that need to be submitted along with the application form are specified on these forms.

All investigators who submit research applications to the YU-RDRC must be qualified by training and experience to conduct the proposed research. In addition, the responsible investigator shall be authorized under Yale University’s U.S. Nuclear Regulatory Commission license to possess and use the specific radioactive drugs proposed in the research. At Yale University, this is accomplished via application to the Yale University Radiation Safety Committee.

All applications submitted to the committee should contain complete answers to all of the questions in the application. Pertinent portions of grants along with a detailed protocol that outlines the entire research procedure should be submitted. All applications must also be accompanied by a completed application to the IRB. The IRB will not grant final approval to a study involving the use of radioactive drugs until the YU-RDRC has provided approval of the formal YU-RDRC application. Any actions taken by the IRB regarding investigations that involve radioactive drugs are reported to the YU-RDRC and the IRB correspondence is filed in the permanent file of the YU-RDRC.

All new submissions are initially screened by the YU-RDRC administrator to determine whether all required documents have been submitted. Each protocol requiring full review by the YU-RDRC is reviewed prior to a committee meeting by at least three committee members, including; one physician with expertise in nuclear medicine, a reviewer with expertise in radiation dosimetry, and a reviewer with radiochemistry/radiopharmacy expertise. In addition, all new protocols involving new PET radiosyntheses (not previously reviewed by the YU-RDRC) will be reviewed by a committee member with expertise in radiopharmacy and radiochemistry.

Protocols subject to the requirements of 21 CFR 361.1 that involve administration of radioactive drugs to research subjects under 18 years of age are also reviewed by one or more *ad hoc* pediatric consultants to the committee, who report their assessment of the protocol in writing.

YU-RDRC will perform full review of all protocols involving new radioactive drugs used for basic physiological or pathophysiological investigations under the conditions specified at 21 CFR 361.1. Such drugs are defined as “generally recognized as safe and effective” (GRASE) and thus exempt from the new drug provisions of the Food, Drug, and Cosmetic Act. This is the specific category of drugs that the RDRC is chartered to approve by the FDA.

The YU-RDRC will review, approve and maintain institutional Drug Master Files (IDMFs) for the radioactive drugs produced in the Yale University Cyclotron Facility. Each IDMF includes, in one place, the required information concerning the chemistry and manufacturing control information for the radioactive drug, as well as documentation of the “no clinically detectable pharmacological effect” level and the radiation dosimetry for the radioactive drug. YU-RDRC applications can incorporate any necessary information in an IDMF by reference to the IDMF.

3. Amendments to Approved Protocols

Any significant alteration of the original proposed research plan requires submission of a request for an amendment to the Committee, the form, “**Application to Involve Human Subjects in Biomedical Research that Includes use of Radioactive Drugs not covered under an IND (2015-1)**” (**Appendix B**), must be used. An amendment is required for any changes in the IRB protocol on annual renewal that has an impact on radiotracer administration. Amendments will be pre-reviewed by representatives on the committee with expertise in the area of change prior to the meeting.

4. Review of Changes in Radioactive Syntheses

Any changes in the radioactive synthesis must be submitted for review by the full committee, and those changes must be outlined in a revised, IDMF, which is submitted with the application amendment.

C. Monitoring Procedures

The YU-RDRC will monitor all active protocols through review of quarterly reports provided by the PI. Content of these reports are listed below. Amendments in any protocol are also reviewed at the regularly held meeting, which will occur at least quarterly.

D. Reporting Procedures

1. Adverse Reaction Reporting

The investigator must report to the YU-RDRC within 24 hours all serious adverse events associated with the use of the radioactive drug during the research study [361.1(d)(8)].

All potential adverse events associated with the use of the radioactive drug in the research study [21 CFR 361.1] must be reported to the YU-RDRC within 3 days, but no later than 7 calendar days.

The RDRC should receive a copy of the PET Center's completed "Adverse Event Report".

The YU-RDRC must report to the FDA all adverse events probably attributable to the use of the radioactive drug in a research study within 7 days. A formal investigation may occur after this initial report, although the results of this investigation must also be reported to the FDA.

Any potential adverse reactions reported by the YU-RDRC to the FDA will also be reported to the IRB of record for the study (e.g., the Yale IRB or external IRB of record).

All potential adverse reactions associated with use of a radioactive drug will be reviewed by the committee at the next available meeting.

See, 21 CFR 361.1(d)(8) (**Appendix E**) and FDA Guidance - **The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application, August 2010 (Appendix F)**.¹

2. Quarterly Reporting

For all protocols subject to the requirements of 21 CFR 361.1, effective September 2018, in addition to annual reporting the principal investigator must report on the progress of the research on the following due dates of each year:

- April 15 (Reporting Period January 1 – March 30)
- July 15 (Reporting Period April 1 - June 30)
- October 15 (Reporting Period July 1 – October 31)
- January 15 (Reporting Period September 1 – December 31)

¹ Specific language from the guidance (**Appendix F**) is as follows: "Adverse reactions. Section 361.1(d)(8) requires that the investigator immediately, but no later than 7 calendar days, report to the RDRC all adverse effects associated with the use of the radioactive drug in the research study. The RDRC must report immediately, but no later than 7 calendar days, to FDA all adverse reactions probably attributable to the use of the radioactive drug in the research study. That is, the RDRC need not confirm a causal relationship between the drug and the event, but a likelihood that the event and the use of the drug were related."

This is performed by submission of a form entitled “**Quarterly Progress Report For RDRC-Approved Research Protocol Subject to Requirements of 21 CFR 361.1**” (Appendix C).

This interim document will need to include:

- A summary of all patients recruited into each protocol and subgroup;
- The number of extra doses of radiopharmaceuticals administered due to technical failures as part of proposed protocol contingencies;
- Any issues related to radiochemistry production and quality assurance; and
- Any potential adverse events. A potential Adverse Event is defined as all events potentially associated with the radiotracer that are not clearly defined in the IRB protocol as expected side effect of other non-radiopharmaceutical drugs, which may be used in the protocol.

3. Reporting IRB Renewal and Study Closure

The RDRC should receive a copy of the IRB annual renewal approval letter, along with a copy of the reapproved consent forms. It is the responsibility of the Principal Investigator (PI) to provide this information to the YU-RDRC within 1 week of receipt of the IRB annual re-approval letter. The PI should also provide the YU-RDRC notification of the close of any research study by providing a copy of the IRB closure letter.

4. FDA Reporting Requirements

4.1. Annual Report

FDA regulations require that the responsible investigator submit an annual report to an RDRC using Form FDA 2915, “**Report on Research Use of Radioactive Drug**” (Appendix D). Completed annual reports must be submitted to the YU-RDRC by 15th of January each year, so that these forms can be reviewed by the Chair, and other committee members as necessary, and forwarded by the RDRC to the Food and Drug Administration by 31st of January. This report contains the following information:

- Name of institution
- Name and address of the IRB
- RDRC committee number
- Title of the research project
- Study ID number and approval/termination dates
- Brief description of the purpose of the research project
- Name of responsible investigator
- Pharmacological dose (including the name of the nonradioactive drug, maximum mass dose of the nonradioactive drug administered per subject in a single dose and per year and per protocol, No-observed-effect level [NOEL] mass dose and route of administration),
- Names of radionuclide(s) used (including any present as significant contaminants)
- Radiation absorbed dose for a representative subject (including the maximum dose commitment to the whole body and to blood-forming organs, lens of the eye, and gonads)
- Calculations or references that were used to estimate these maximum dose commitments

- The report shall include the dose contribution of both the administered radionuclide(s) and any x-ray procedures associated with the study
- Listing of the following information for each subject enrolled during the year:
 - Age, sex, approximate weight, the total activity of each radioactive drug administered and other associated procedures
 - Total absorbed dose per single administration for each radioactive study drug and the total dose per organ per year.

The YU-RDRC will add the names and qualifications of members of the committee and any consultants used by the YU-RDRC during the review of studies over the past year to the annual report submitted to the FDA.

Protocols will be placed on temporary hold for recruitment if the quarterly or annual reports are not provided by the deadlines defined in the YU-RDRC Policies and Procedures Manual. The temporary hold will be lifted once all compliant documents are received.

4.2. Special Summary Report

For any protocol subject to the requirements of 21 CFR 361.1 that involves either more than 30 subjects or subjects under 18 years of age, a special summary must be submitted to the FDA no later than 7 calendar days post YU-RDRC and IRB approval, using **FDA Form 2915** as outlined above (**Appendix D**). The responsible physician must provide the YU-RDRC with a completed FDA Form 2915 for each such protocol as a condition for final approval by the YU-RDRC.

4.3. Protocols with RDRC Oversight involving IND Drugs

For any protocol, which involve both RDRC oversight and IND drugs, a summary of the RDRC-protocol results shall be included in the IND annual reports and/or periodic FDA submissions. The FDA 21 CFR 361.1 (e) states: “The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to part 312 of this chapter shall be included in the submissions required under part 312 of this chapter.”

The RDRC should receive either a) copy of the IND submissions, or b) the PI must provide confirmation of compliance with this regulatory requirement.

E. YU-RDRC Record Retention

YU-RDRC records will be retained for three (3) years after closure of a protocol or, for those studies subject to the requirements of 21 CFR 361.1, for three (3) years after FDA was notified of closure of the protocol by submission of FDA Form 2915. After protocol closure, records may be retained either as original paper documents or as scanned electronic documents (pdf files).

APPENDICES

Appendix A.	<u>YU-RDRC Membership</u>
Appendix B.	<u>YU-RDRC Application</u>
Appendix C.	Quarterly Report Form
Appendix D.	<u>FDA Form 2915</u>
Appendix E.	<u>FDA Regulations - 21 CFR 361.1</u>
Appendix F.	<u>FDA Guidance - The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application, August 2010.</u>
Appendix G.	<u>Yale HRPP 940 GD.1, Guidance on Committee Reviews Required for Human Subjects Research Protocols Using Radiation.</u>

REFERENCES

FDA – Radioactive Drug Research Committee (RDRC) Program:
<https://www.fda.gov/drugs/scienceresearch/ucm574871.htm>